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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 10/692,303      | 10/23/2003  | Thomas Primiano      | 02-1133-C           | 7346             |

7590 12/17/2007  
McDonnell Bochnen Hulbert & Berghoff  
32nd Floor  
300 S. Wacker Drive  
Chicago, IL 60606

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| EXAMINER |
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BRISTOL, LYNN ANNE

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| ART UNIT | PAPER NUMBER |
|----------|--------------|

1643

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| MAIL DATE | DELIVERY MODE |
|-----------|---------------|

12/17/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Office Action Summary**

Application No.

10/692,303

Applicant(s)

PRIMIANO ET AL.

Examiner

Lynn Bristol

Art Unit

1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 01 October 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-9 is/are pending in the application.
- 4a) Of the above claim(s) 1-7 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 8 AND 9 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

1. Claims 1-9 are all the pending claims for this application.
2. Claim 8 was amended in the Response of 10/1/07.
3. Claims 1-7 are withdrawn from consideration.
4. Claims 8 and 9 are all the pending claims under examination.
5. Applicants' amendments to the claims have not overcome all of the rejections and have raised new grounds for rejection. **This action is FINAL.**

#### **Withdrawal of Rejections**

##### ***Claim Rejections - 35 USC § 112, first paragraph***

##### ***New Matter***

6. The rejection of Claim 8 under 35 U.S.C. 112, first paragraph, for reciting new matter (i.e., "wherein" clause for a negative proviso) is withdrawn.

Applicants' amendment of Claim 8 to delete the "wherein" clause: "wherein the antibody is not conjugated to a radionucleotide or toxin", overcomes the rejection.

Applicants' comments on p. 6 of the Response of 10/1/07 are acknowledged.

##### ***Claim Rejections - 35 USC § 102***

7. The rejection of Claim 8 under 35 U.S.C. 102(b) as being anticipated by Izumoto et al. (Can Res. 56:1440-1444 (1996); cited in the IDS of 3/1/07) is withdrawn.

The amendment of Claim 8 to recite that an unconjugated, humanized anti-L1CAM antibody inhibits cell proliferation of neurological-derived tumors overcomes the rejection.

Applicant's allegations on p. 7 of the Response of 10/1/07 are acknowledged.

***Claims-35 USC § 103***

8. The rejection of Claim 8 under 35 U.S.C. 103(a) as being unpatentable over Rathjen et al. (EMBO J. 3:1-10 (1984)) in view of Cleland et al. (J. Pharm. Sci. 90:310-321 (2001)) is withdrawn.

The amendment of Claim 8 to recite that an unconjugated, humanized anti-L1CAM antibody inhibits cell proliferation of neurological-derived tumors overcomes the rejection.

Applicant's allegations on pp. 7-8 of the Response of 10/1/07 are acknowledged.

***Rejections Maintained***

***Claims - 35 USC § 112, first paragraph***

***Enablement***

9. The rejection of Claims 8 and 9 under 35 U.S.C. 112, first paragraph, in lacking enablement for using any unconjugated, humanized L1CAM antibody to inhibit proliferation of a tumor cell of neurological origin is maintained.

Applicant's allegations on pp. 4-6 of the Response 10/1/07 have been considered but are not persuasive.

In ¶2 on p. 5 of the Response, Applicants allege that at the time of application filing, at least two antibodies, Herceptin and the I-conjugated L1CAM antibody of Hoefnagel, demonstrated successful uses in vivo.

The Herceptin antibody is directed to an altogether different and non-analogous antigen from the Hoefnagel antibody and used for a specifically different tissue target, namely breast cancer (Her-2/neu) versus brain or neuronal tumor (L1CAM) (discussed in the specification at [0012] citing "Harries and Smith, 2002, Endocr. Relat. Cancer 9: 75-85"). Thus any discussion of Herceptin antibody is irrelevant to the instant enablement rejection for a therapeutic use of an unconjugated L1CAM antibody. It has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992).

Further, Hoefnagel showed with the single L1CAM antibody- I-labeled, chimeric CE7 (chCE7), that it reduced *subcutaneous tumor growth* for a human xenograft neuroblastoma in nude mice (p. 363, Col. 2, ¶1). Hoefnagel did not show that the chimeric antibody could inhibit cell proliferation of the neuroblastoma tumor cell or that an unconjugated chCE7 antibody was effective. Hoefnagel does not show that the chCE7 antibody can inhibit proliferation of any L1CAM-expressing neurological tumor cell in any part of the body including the brain (i.e., that the antibody could cross the

blood brain barrier). Thus Applicants can cite to only one example of an in vivo model showing a neuronal tumor-affecting L1CAM antibody but which does not meet the requirements of the instant claimed anti-L1CAM antibody.

In ¶3 on p. 5 of the Response, Applicants allege in vitro experimentation has become a conventional method to find successful agents for cancer treatment. Therefore, Applicants are not required to provide the type of evidence required, inter alia, by the FDA for approval of a new drug, and showing antibodies work in an acceptable in vitro model system does not require administration to humans or animals for enablement.

The Examiner respectfully resubmits that in no instance have applicants been required to meet the safety and efficacy standards of the FDA. Applicants are requested to identify the exact page, paragraph and line in any of the previous Office Action(s) where any such requirement has been imposed. To reiterate, Reichert et al. (Nat. Biotech. 23(9):1073-1078) is cited for showing the number of clinically successful antibody immunotherapeutics and to provide background and guidance regarding the challenges facing immunotherapeutics at the time of application filing.

Applicants further assert that in vitro methods are conventional for drug testing. However, pursuant to MPEP 2144.03, "ordinarily there must be some form of evidence in the record to support an assertion of common knowledge." Applicants have provided no such evidence to substantiate their assertion.

Further, inasmuch as in vitro drug testing *may be* a platform technology in a determination of enablement, the complexity and difficulty of antibody delivery for

cancer treatment is underscored by Voskoglou-Nomikos (Clin. Can. Res. 9:4227-4239 (2003)). Voskoglou-Nomikos conducted a study using the Medline and Cancerlit databases as source material in comparing the clinical predictive value of three pre-clinical laboratory cancer models: the in vitro human cell line (Figure 1); the mouse allograft model; and the human xenograft model (Figures 2 and 3). Significantly when each of the cancer models was analyzed against Phase II activity, there was a negative correlation for the in vitro human cell line models being predictive of good clinical value. No significant correlations between preclinical and clinical activity were observed for any of the relationships examined for the murine allograft model. And the human xenograft model showed good tumor-specific predictive value for NSCLC and ovarian cancers when panels of xenografts were used, but failed to predict clinical performance for breast and colon cancers. Voskoglou-Nomikos suggests that "the existing cancer models and parameters of activity in both the preclinical and clinical settings may have to be redesigned to fit the mode of action of novel cytostatic, antimetastatic, antiangiogenesis or immune-response modulating agents" and "New endpoints of preclinical activity are contemplated such as the demonstration that a new molecule truly hits the intended molecular target" (p.4237, Col. 1, ¶16).

Applicants cannot rely on the prior art to establish enablement for the claimed pharmaceutical composition comprising any unconjugated anti-L1CAM antibody having a neuronal-tumor cell proliferation inhibitory effect in vivo. Applicants cannot rely on their own specification for showing a pharmaceutical composition comprising *any*

unconjugated anti-L1CAM antibody having a proliferation inhibitory effect on any neuronal-tumor cell in vivo much less in any human.

In ¶4 on p. 5 to ¶11 on p. 6 of the Response, Applicants allege that because Reichert discloses a limited number of monoclonal antibodies are FDA approved, that FDA standards of approval are improperly implicated in the enablement rejection. Then Applicants rely on Reichert as allegedly supporting the instant claims where "approval success rates for chimeric and humanized antibodies are consistently 18-29%" and "most monoclonal antibodies studies were for treatment of oncological and immunological indications and FDA approved antibodies in these two categories comprise 89% of total approved monoclonal antibodies (p. 1076, para 2).

See the discussion supra regarding the Examiner's interpretation of Reichert. Finally, Reichert does not teach or suggest an example of a L1CAM antibody for inhibiting neuronal-tumor cell proliferation.

In ¶2 on p. 6 of the Response, Applicants allege that in amending the claims to recite that the L1CAM antibody is humanized, that the claims would be more enabled than otherwise.

In the absence of an art recognized neuronal tumor cell inhibitory effect in vivo in any animal for any unconjugated, humanized anti-L1CAM antibody much less for the commercial anti-L1CAM antibodies of the instant specification (i.e., 5G3 (PharMingen) and UJ127 (NeoMarkers)), one of ordinary skill in the art could not reliably, reproducibly and predictably use any unconjugated, humanized anti-L1CAM antibody in a pharmaceutical composition to treat any neuronal tumor.



**New Grounds for Rejection**

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 8 and 9 are indefinite for the recitation "treating a tumor by inhibiting proliferation of a tumor cell of neurological origin that expresses L1CAM" in Claim 8 because it is not clear what the relationship is between the "tumor" and the "tumor cell of neurological origin". Is the intention to treat a neural tumor by targeting L1CAM<sub>v</sub> expressing neuronal tumor cell proliferation with the L1CAM antibody? As presently interpreted, antibody targeting of any L1CAM-expressing tumor cell of neurological origin would apparently result in the treatment effect on any kind of tumor.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Umana et al. (Nat. Biotech. 17:176-180 (1999)).

Claims 8 and 9 are interpreted as being drawn to a pharmaceutical composition for treating an L1CAM-expressing tumor comprising an unconjugated, humanized anti-L1CAM antibody or a fragment thereof that inhibits a L1CAM-expressing neuronal tumor cell and a pharmaceutically acceptable excipient (Claim 8) where the antibody recognizes human L1CAM (Claim 9).

Applicants specification supports but does not define a "humanized" antibody thus it is understood as encompassing any anti-L1CAM antibody that has been engineered to contain a human portion such as an Fc domain.

Umana discloses an unconjugated, chimeric chCE7 antibody (a chimeric mouse anti-human L1CAM Mab) that has been modified in the Fc portion to produce glycoform variants express increasing amounts of bisected complex oligosaccharides. Umana shows that increasing ADCC activity of the variants correlates with the level of Fc-associated, bisected complex oligosaccharide as measured by in vitro lysis of neuroblastoma cell lines in the presence of human lymphocytes (Fig. 5B). Umana discloses "the boosted ADCC activity of the bisected chCE7 glycoforms make this unconjugated Mab an interesting candidate reagent for treatment of neuroblastoma" (p. 179, Col. 2, ¶2). Umana discloses preparing the antibodies in a pharmaceutical preparation for treating a neuronal tumor. One skilled in the art would readily envisage that the chimeric L1CAM antibody variants of Umana would read on and therefore

anticipate the unconjugated, humanized anti-L1CAM antibody of the instant pharmaceutical composition for the reasons set forth above.

The claimed antibody appears to be the same as the prior art antibodies, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See *In re Best* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

### ***Conclusion***

12. No claims are allowed.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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LARRY R. HELMS, PH.D.  
SUPERVISORY PATENT EXAMINER